UNIVERSITY OF MICHIGAN
DOES NOT CIRCULATE
SEP 13 1955
MEDICAL LIBRARY

ACTA PHYSIOLOGICA SCANDINAVICA

VOL. 33 SUPPLEMENTUM 119

THE FUNCTION OF THE VENTRICLES OF THE HEART

Studies on the Relation Between Diastolic Filling and Ventricular Work in the Anesthetized Dog

By

ERIK BERGLUND

STOCKHOLM 1955

UNIVERSITY OF MICHIG
MEDICAL LIBRARY

ACTA PHYSIOLOGICA SCANDINAVICA
VOL. 33 SUPPLEMENTUM 119

From the Department of Physiology, Harvard School of Public Health, Boston, Massachusetts, U.S.A.

THE FUNCTION OF THE VENTRICLES OF THE HEART

Studies on the Relation Between Diastolic Filling and Ventricular Work in the Anesthetized Dog

BY

ERIK BERGLUND

STOCKHOLM
ALB. BONNIERS BOKTRYCKERI
1955

The present publication is based mainly on studies reported in the following papers:

1. SARNOFF, S. J. and BERGLUND, E.: *Ventricular Function. I.* Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation, 1954, *9:* 709–718.
2. CASE, R. B., BERGLUND, E. and SARNOFF, S. J.: *Ventricular function. II.* Quantitative relationship between coronary flow and ventricular function with observations on unilateral failure. Circulation Research, 1954, *2:* 319–325.
3. ISAACS, J. P., BERGLUND, E. and SARNOFF, S. J.: *Ventricular Function. III.* The pathologic physiology of acute cardiac tamponade studied by means of ventricular function curves. Am. Heart J., 1954, *48:* 66–76.
4. BERGLUND, E., SARNOFF, S. J. and ISAACS, J. P.: *Ventricular Function. IV.* Role of the pericardium in the regulation of cardiovascular hemodynamics. Circulation Research, 1955, *3:* 133–139.
5. SARNOFF, S. J., CASE, R. B., BERGLUND, E. and SARNOFF, L. C.: *Ventricular Function. V.* The circulatory effects of Aramine; mechanism of action of "vasopressor" drugs in cardiogenic shock. Circulation, 1954, *10:* 84–93.
6. BERGLUND, E.: *Ventricular Function. VI.* Balance of left and right ventricular output: Relation between left and right atrial pressures. Am. J. Physiol., 1954, *178:* 381–386.
7. CASE, R. B., BERGLUND, E. and SARNOFF, S. J.: *Ventricular Function. VII.* Changes in coronary resistance and ventricular function resulting from acutely induced anemia and the effect thereon of coronary stenosis. Am. J. Med., 1955, *18:* 397–405.
8. SARNOFF, S. J. and BERGLUND, E.: *The Potter Electroturbinometer.* An instrument for recording total systemic blood flow in the dog. Circulation Research, 1953, *1:* 331–336.

9. SARNOFF, S. J., BERGLUND, E. and WAITHE, P. E.: The measurement of systemic blood flow. Proc. Soc. Exper. Biol. & Med., 1952, *79:* 414–416.

In the text these will be quoted as (1) and (2), etc.

Doctors STANLEY J. SARNOFF, ROBERT B. CASE and JAMES P. ISAACS have shared in the planning and performing of experiments and in the development of methods.

Mr. PHILIP E. WAITHE, Mrs. L. C. SARNOFF, Doctors HANS BORST and FRANK DUFF, Mr. LOUIS FRENI and Mr. HERBERT KAUFMAN have given valuable assistance in the experiments.

Miss ELEANOR GOTZ performed the blood gas analyses, assisted in the analysis of data, and prepared the figures.

The figures were photographed by Miss STEFANA PULEO.

The author is also grateful to Mr. DAVID POTTER for generous redesigning of the electronic flowmeter for physiological use, and to Doctors JAMES L. WHITTENBERGER and WALTER T. GOODALE for experienced advice and stimulation.

Contents

"The heart possesses in a high degree the power of adaptation to changed conditions, which is the essential characteristic of living organisms; and we have now to see how far we can refer this power to the physiological mechanisms with which the heart is endowed." E. H. STARLING, 1897.

Introduction

A relationship between resting or diastolic muscle fiber length and force of contraction has been demonstrated in ventricular muscle strips, isolated perfused hearts and heart-lung preparations. The aim of the present study, at the time of its initiation in 1952, was to find out whether the same relation between diastolic filling and ventricular work existed in the living animal. Later, the project was extended to examine—

1) the circumstances in which the classically conceived descending limb of the "Starling curve" occurs,

2) the effect on cardiovascular dynamics of impaired oxygen transport to the heart,

3) the cardiovascular effects of the normal or altered pericardium,

4) the mechanism of ventricular output balance during various hemodynamic states, and

5) a method for assaying the cardiovascular effects of drugs, especially with regard to means for differentiating the cardiac and peripheral vascular effects.

After a review of the early work in this field the findings are summarized and discussed in the section "Present Investigation." This is followed by a general discussion.

Development of the Concept of Starling's Law of the Heart

The field of hemodynamic studies was opened in 1733 when STEPHAN HALES measured arterial and venous pressures of a horse "caused to be tied down alive on its back." When the animal strained to get loose, the arterial pressure rose, for the blood was "impelled from all parts (of the body) to the vena cava, and consequently, there was a greater supply for the heart, which must therefore throw out more at each pulsation, and thereby increase the force of the blood in the arteries." Hemorrhage was performed in steps, and when enough blood had been evacuated, the blood pressure fell and the pulse was weak and quick. "And the diastole of the heart must necessarily be proportionately small, for if the heart dilated as much when a small quantity of blood flowed into the ventricle as when a large quantity entered, it must then consequently be filled with air each time, which would soon cause the death of the animal." From detailed volumetric studies of the ventricles in the dead animal, Hales also tried to estimate the stroke volume of the heart.

The work of WEBER (1846), HEIDENHAIN (1864) and FICK (1867) demonstrated a relationship between resting length, tension and energy production of striated skeletal muscle. This work stimulated others (BLASIUS, 1872; DRESER, 1887; FRANK, 1895) to examine whether heart muscle behaved in a similar fashion; for this purpose they studied the performance of isolated frog hearts. Although both Blasius' and Dreser's work indicated a relation between the volume and pressure in diastole and the force of contraction during the following systole, this was demonstrated most clearly by Frank. The latter also stated that mechanical factors other than the fiber length are of importance for the performance of the heart.

During the following decades the experimental work in this field was further applied to the mammalian heart. Studies were performed on living animals, heart-lung preparations or isolated perfused hearts. The filling pressure of one or both ventricles was measured (as atrial

pressure or as diastolic ventricular pressure). It was not possible, however, to estimate the volume of each ventricle separately; instead, the total volume of the two ventricles was obtained. The stroke output was obtained by direct measurements or simple flowmeters in the isolated heart or heart-lung preparation; in the living animal it was usually estimated from the arterial pulse contour (WIGGERS, 1914) or by means of ventricular plethysmography (ROY and ADAMI, 1888; HENDERSON, 1906).

WALLER (1878) studied the response of right and left atrial pressures to acute occlusion of the ascending aorta in mammals, before and during spinal cord stimulation. The left atrial pressure rose markedly, much more than the right. His explanations was "... jedesmal, wenn der linke Ventrikel gezwungen wird, unter erhöhtem Drucke zu arbeiten, muss er, um dieses zu können, reichlich und unter stärkerer Spannung gefüllt sein; dieser Bedingung ist aber nur dann zu genügen, wenn das Blut aus den erweiterten Lungenvenen unter höherem Drucke hervorquillt."

Using the mammalian heart-lung preparation developed by NEWELL MARTIN (1883), HOWELL and DONALDSON (1884) studied the effect of changing the venous pressure and the arterial resistance. With increased venous pressure the stroke work of the heart increased. "It is certain that the most direct factor influencing the quantity of blood sent out from the ventricle, and hence the work done by the ventricle, is the intraventricular pressure by which the ventricle is distended during diastole." Varying the arterial pressure from 58 to 147 mm. Hg (by aortic constriction) did not affect stroke volume. Their explanation was that "as the load increases, a greater amount of energy is liberated, in consequence of some change in the molecular state of the ventricular muscle associated with increased tension at the commencement and during the early stage of its contraction. ... the extent of the contraction is unchanged [and] the most probable interpretation of this fact is that the contraction in each case is maximal, and completely empties the ventricular cavity." This latter view (about the complete systolic emptying) was in line with that held by ROY (1879) after studies on the frog heart; it was, however, contrary to views held by HARVEY (1628), and later by ROY and ADAMI (1888), JOHANSSON and TIGERSTEDT (1889), and FRANK (1895).

HENDERSON (1906) demonstrated in the isolated heart that when

the left ventricle is not distended by fluid, it "lies in a contracture. When fluid is supplied through the auricle under a few cm. of pressure, this part of the heart begins to beat vigorously." This was interpreted as an additional indication of the fundamental identity in the properties of skeletal and cardiac muscle. In the same type of preparation Henderson and PRINCE (1914) found that the work of each ventricle varied with the filling of the same ventricle, and this relation was, at least up to a certain limit, independent of the filling of the other ventricle. It was, however, Henderson's belief, based on cardiometric studies in the open-chest dog that the filling of the ventricle was maximal at the venous pressures normally encountered, and that the cardiac output therefore varied only as a function of the heart rate. KROGH and LINDHARD (1912) and KROGH (1912) on the other hand found it inconceivable that changes in heart rate could fully account for the large variations in cardiac output which they found in man during exercise. They assumed that the changes in stroke volume were due to changes in diastolic size.

The results obtained during the next few years by STARLING *et al* in England, STRAUB in Germany, and WIGGERS in U.S.A., were all in general agreement, but varied in details, mainly due to differences in method and choice of values to be measured.

An improved heart-lung preparation (JERUSALEM and STARLING, 1910; KNOWLTON and STARLING, 1912) was used extensively by Starling's group as well as by Straub. In both laboratories it was found that right and left ventricular work was increased by a greater venous inflow from the right atrial reservoir. This was accompanied by an increase in diastolic size of the ventricles (KNOWLTON and STARLING, 1912; PATTERSON and STARLING, 1914; PATTERSON, PIPER, STARLING, 1914, and STRAUB, 1914). Starling's group emphasized that beyond a certain degree of diastolic filling, there was a marked fall in ventricular work—the classical descending limb of the Starling curve.

Further, when the arterial resistance was increased, there was a marked elevation of left ventricle work together with a marked increase in heart size. Straub observed that right atrial pressure and right ventricular diastolic pressure were essentially unchanged while the corresponding pressures on the left side were increased; this indicated that the increased heart size was mainly due to dilation of the left ventricle, and that this dilation was a sign of the elastic properties of the ventricle. He stated that the "tension"

—produced largely by the atrial systole—was a more important determinant of the power of contraction than the diastolic volume; this relation between resting pressure and contractile force was found also for the atrial contraction. On the other hand, Patterson, Piper and Starling considered the rise in left ventricle end-diastolic pressure insignificant and emphasized that the marked increase in heart size was not accompanied by any rise in filling pressure (measured as *right* atrial pressure). On this erroneous basis they denied the importance of "initial tension" stating: "In every case, therefore, the reaction of the heart muscle seems to be determined by the length of its constituent fibers at the moment of activity. Changes in initial tension are merely incidental to changes in length." *"... the law of the heart is therefore the same as that of skeletal muscle, namely that the mechanical energy set free on passage from the resting to the contracted state depends on the area of chemically active surfaces, i.e., the length of the muscle fibers."* (Later slightly reformulated by STARLING, 1915.)

WIGGERS (1914) recorded pressures in right atrium and right ventricle in the open chested dog; the right ventricular power was deduced from the right ventricle pulse contour. Saline infusion was followed by increased "initial, intraventricular tension" (measured as end-diastolic pressure) and increased steepness of the ascending limb of the right ventricular pressure curve as well as increased right ventricular systolic pressure "showing that [the mammalian ventricle] follows the law of the isometric curve established by Frank for the frog's ventricle." He also found an increased contractility with adrenalin.

Data indicating that the effective ventricular filling pressure, and therefore the initial fiber length, rather than the absolute level of diastolic pressure in the ventricle, was the determinant factor, were presented by EVANS and MATSUOKA (1915), KUNO (1915) and KATZ (1928). Using the heart-lung preparation, Kuno found that pericardiotomy was accompanied by lower filling pressures and higher maximal work of both ventricles. Evans and Matsuoka, using the same type of preparation, demonstrated that the increased work output after pericardiotomy was accompanied by increased diastolic volume and lower right atrial pressure. Katz enclosed a turtle heart in a fluid-filled chamber in such a way that the volume of the heart could be varied independently of the absolute pressure in the ventricular

cavity and vice versa; the force of the isometric contraction varied with the volume but not with the *absolute* pressure.

A relation between diastolic ventricular volume, ventricular work and oxygen consumption was demonstrated by several workers. ROHDE (1912) used the isolated perfused mammalian heart, and found that the work and oxygen consumption of the left ventricle had a maximum at a certain diastolic volume. EVANS and MATSUOKA (1915), using the heart-lung preparation, demonstrated that an increase of the cardiac output and/or arterial pressure was accompanied by increased oxygen consumption; further, there was "a parallel between the oxygen usage of the heart and the heart volume, i.e., the length of the cardiac fibers." This was confirmed by STARLING and VISSCHER (1927) who also found that when the "descending limb" of the "Starling curve" was reached, the oxygen consumption continued to rise with the increasing heart volume in spite of the simultaneous fall in mechanical work.

Numerous studies have subsequently been done with the aim of finding out whether "Starling's Law" is valid and/or significant in the living animal or man. The conclusions have been less uniform in these studies and include the belief that "Starling's Law" is not valid in the normal living animal (for references, see 1).

Present Investigation

Method

The method has been described in detail (1–9, especially 1). It may be briefly summarized as follows: In anesthetized dogs the chest was opened for the insertion of flowmeters; 2–4 ribs (in later experiments 1–2 ribs) on the left side were removed. An electronic flowmeter (8) was connected to the aorta for measurement of systemic blood flow (cardiac output minus coronary flow) (9). In some experiments (1, 2, 7) left coronary artery flow was also measured with a recording rotameter. Mean pressures were obtained via catheters from the left and right atria, the pulmonary artery and aorta, and measured with electrical capacitance manometers. All these values were continuously recorded on a direct-writing oscillograph. A reservoir was connected to the right or left atrium or to the femoral vessels; it was filled with donor dog blood and/or dextran. By means of this reservoir the blood volume of the dog, and thus the atrial pressures, could be easily varied. High cervical vagotomy was performed in more than half of the experiments, in order to keep the heart rates at a steady level, usually between 160 and 200/min.

In one dog the aortic flowmeter was inserted directly in the aorta, and the chest was closed before the hemodynamic data were obtained; the pressure in the ventral part of the chest of this dog was measured with an electrical capacitance manometer.

In four experiments samples of coronary sinus blood were taken for analysis of the oxygen content (2, 7). In these and several other experiments the arterial oxygen content and capacity were also measured. The left coronary artery blood flow was restricted by constriction of the tubing leading to the left coronary artery cannula. Pericardial tamponade was produced by injecting saline or air into the pericardial cavity; in those experiments the intrapericardial pressure was measured with the electrical capacitance manometer.

Data for "ventricular function curves" (modified Starling curves) were obtained by increasing the atrial pressures in steps until the left

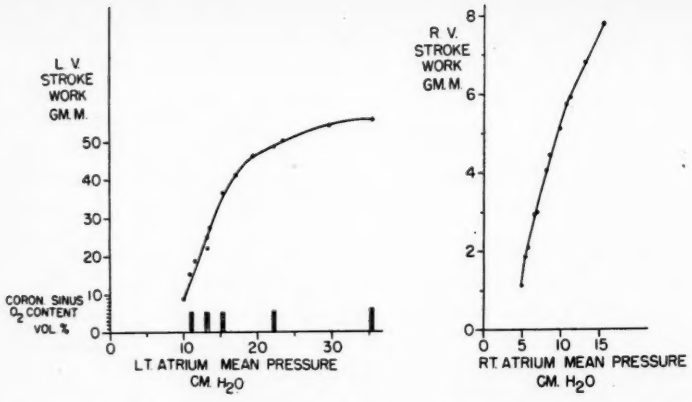

Figure 1: Exp. No. 107. Dog weight 17.2 kg. Heart weight 130 gm. Same experiment as in ref. 7, table I, No. 107. Vagi cut. Pericardium intact. Left and right *ventricular function curves.* The bars at the bottom denote the coronary sinus oxygen content from samples taken at these various points of the ventricular function curve. The simultaneous arterial oxygen contents were 15.9—16.9 volumes per cent. Note that the coronary sinus content did not fall even at high work loads. See text.

atrial pressure had reached 35—50 cm. H_2O. This procedure was done repeatedly in each dog. Values for calculation of the work of the ventricles were taken one-half to one minute after each infusion. The mechanical work per stroke of each ventricle was calculated by multiplying the stroke volume by the difference between the arterial and atrial pressures.

Simultaneous left and right *ventricular function curves* were then constructed by plotting the ventricular stroke work against the simultaneous mean atrial pressure on the same side. (See Figure 1.)

Discussion of Method

The experiment involves the use of anesthesia and anticoagulants, extensive surgical procedure, artificial respiration, and the adding of donor dog blood and/or dextran. Further, a flowmeter (8) is inserted in the aorta (1, 9) and the left main coronary artery is sometimes cannulated (2, 5, 7).

Care is taken to minimize the consequences of these factors. In early experiments the arterial oxygen saturation was not always satis-

factory; this was subsequently avoided by frequent hyper-inflation of the lungs and by keeping the end-expiratory pressure above 4 cm. H_2O when the chest was open. The aortic flowmeter used in most of the early experiments (No. 1—82) was the $^3/_8$-inch diameter unit described in (8). The high resistance imposed by this unit was undesirable. In most of the later experiments we used units with a much smaller pressure-drop (one-half-inch unit with 15 mm. Hg pressure drop at 5 liters blood flow/min., and $^7/_{16}$-inch unit with 25 mm. Hg at 5 liters blood/min.).

As stated above, the left atrial pressures, and consequently the pulmonary capillary pressures, are often raised acutely to levels, which if maintained would produce pulmonary edema. The disadvantage of this for the condition of the animal is realized, but the examination of the myocardial behavior at high filling pressures may reveal changes in myocardial contractility, which are not otherwise readily apparent (2).

The validity of use of mean atrial pressure as an index of the end-diastolic ventricular pressure has been previously discussed (1). First, it is difficult to obtain consistently artefact-free ventricular pressure tracings through catheters, especially at the high heart rates frequently encountered in our experiments. Second, simultaneously obtained mean atrial and end-diastolic ventricular pressures at various pressure levels showed good correlation, and were not more than 3 cm. H_2O apart even at levels of 40 cm. H_2O. When regurgitation through the atrioventricular valve occurs, the mean atrial pressure does not reflect the end-diastolic ventricular pressure; care has been taken to exclude such values.

The reasons for using the relation between atrial pressures and ventricular stroke work as the index of ventricular function and myocardial contractility have been discussed in reference 1.

Usually during standard conditions the ventricular function curves were reproducible within a narrow range; exceptions, especially on the lower part of the ventricular function curves were sometimes noted in the early part of an experiment. There was a considerable variability in the work performance of hearts in the various dogs, even when considered per weight heart or ventricles. Quantitative comparisons were therefore always made only in the same dog. Control curves were obtained before and after an "intervention curve" (coronary constriction, adrenalin, etc.).

The advantages of the method are mainly in the continuous recording of simultaneous pressure and flow values. This makes it possible to, 1) analyze rapid changes in cardiovascular events; 2) more easily estimate when a steady state of pressures and flows is present; 3) vary the filling pressures over a wide range in a few minutes and analyze the responses to this maneuver, and 4) differentiate the cardiac and peripheral vascular effects of drugs.

Results

Relation Between Diastolic Filling and Ventricular Stroke Work

This relation has been presented as left and right *ventricular function curves* (1), obtained by plotting the stroke work of the ventricle against the simultaneous mean pressure in the atrium on the same side. The general shape of "normal" left and right ventricular function curves is shown in Figure 1.

The initial part of the curve is very steep, i.e., a small increment in filling pressure is accompanied by a very marked increase in ventricular stroke work. At higher levels of atrial pressures there is a leveling of the curve, and a range is reached where marked changes in filling pressure do not markedly change ventricular stroke work. There is no significant descending limb, i.e., there is no significant fall in stroke work although the left atrial pressure is increased to as high as 50 cm. H_2O (1, 4). The height and shape of the function curve of a given ventricle can be altered by a number of factors (1).

The increased work is accompanied by a larger oxygen consumption. This increased amount of oxygen is supplied by higher coronary blood flow rather than by more complete oxygen extraction from the coronary blood (7). Thus the oxygen content of the coronary sinus blood does not fall when the work load is increased (Fig. 1).

It was thought that the maximum work value of the "normal" ventricular function curve, i.e., the maximum work output of the ventricle under the described conditions, might be limited by the maximum rate of oxygen delivery to the myocardium. However, when the coronary blood flow was artificially increased by means of a pump, in a dog with a normal heart and a normal hematocrit, the maximum

work limit was unchanged (7). Contrariwise the same maneuver, when performed in dogs with low ventricular function curves due to marked anemia, did increase left ventricular work and lower the filling pressure. The studies reported in (7) indicate that even at high work loads the coronary arteries have a significant vasodilator reserve, provided the oxygen content of the arterial blood is normal. Further, the oxygen extraction in the normal dog with a normal arterial content is high, but not, as often stated, maximal; during the increased work at the higher part of the ventricular function curve the coronary sinus oxygen content does not fall significantly (7). (See Figures 1 and 3.) On the other hand, when the stress of coronary constriction or marked anemia (or both) is added, the coronary sinus oxygen content may fall (2, 7). (See Fig. 3.)

It thus seems that the work limit under normal conditions is due to factors in the heart muscle itself rather than to a limitation of the oxygen supply to it. There are several possible reasons for the fact that ventricular work does not increase further after a certain filling pressure has been reached. One such factor is the pressure-volume relation of the ventricles (1, 3); it is probable that, at the higher levels of filling pressure, further increments of pressure do not significantly increase the diastolic volume and fiber length; consequently the increase in work would be insignificant. Secondly, it is possible that the fiber length continues to increase without any further increase in contractile force; this is consistent with the observation that, at a certain length, the contractile force of cardiac muscle strips reaches a maximum (LUNDIN, 1944).

The data reported in (3) and in a following section (Pericardium) demonstrate that it is the effective filling pressure (atrial pressure minus ambient pressure) which determines the ventricular stroke work. This is consistent with the concept that the diastolic volume and fiber length, rather than the absolute pressure in the ventricle during diastole, determines the force of contraction.

It is important to note that very small changes in effective filling pressure on the lower part of the ventricular function curve, are accompanied by large changes in ventricular work. Respiratory variations of extra-cardiac pressures may thus significantly affect ventricular work.

In one experiment ventricular function curves were obtained after the chest had been closed; the dog was breathing spontaneously. The

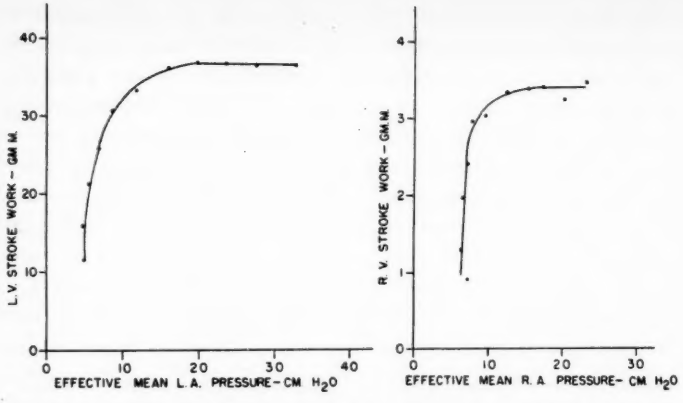

Figure 2: Exp. No. 115. Dog weight 16.0 kg. Heart weight 118 gm. Vagi and pericardium intact. *Ventricular function curves obtained after closure of the chest.* The dog was breathing spontaneously. The "effective atrial pressures" are the pressures measured in the ventral part of the chest subtracted from the atrial pressures.

results are shown in Figure 2. The ventricular work values are plotted against effective atrial pressures, i.e., the atrial pressure minus the intrapleural pressure. The steepness of the lower part of the curve is undoubtedly influenced by small errors in the measurement of effective atrial pressures; these errors are due to difficulties in measurement of intrapleural pressure. The intra-pericardial pressure at the end of diastole, although more desirable, is even more difficult to measure accurately.

The "Descending Limb" of Ventricular Function Curves

In the "normal" ventricular function curves no significant descending limb was observed. This was the case also in the presence of a high aortic resistance even when the left effective filling pressure was increased to as much as 50 cm H_2O (1, 4). A significant descending limb was found only during the following circumstances: a) when valvular regurgitation (4) or marked cardiac irregularities were present; b) when the myocardial oxygen supply was impaired by means of restriction of the left coronary artery flow or marked anemia (1, 2, 7).

This absence of a descending limb in the "normal" heart is at variance with the classically conceived "Starling curves" which showed

a marked fall in ventricular work at higher degrees of filling (STARLING's group, KUNO, STARLING and VISSCHER). However, even Starling's group recorded some experiments in which the left atrial pressure was increased to as high as 40 cm. H_2O without a fall in ventricular work (PATTERSON and STARLING). Unfortunately, in most of their experiments, they did not measure left atrial pressure, and it is possible that this rose to pulmonary edema levels; the consequent hypoxia and restriction of myocardial oxygen supply could have produced a fall in stroke work (2, 7). From the published tracings it seems probable that at least some of the "descending limbs" were due to regurgitation, especially in those experiments in which the pericardium was open (See Ref. 4).

The author does not wish to deny that a true descending limb might be obtained in a normal heart if the filling pressure could be raised sufficiently without the occurence of regurgitation, arrythmia or pulmonary edema. Such a finding would be consistent with the fact that isolated ventricle muscle strips show a descending limb when stretched beyond a certain limit (LUNDIN, 1944).

Effect of Impaired Oxygen Transport to the Heart

Coronary Artery Constriction

Reduction of left coronary artery flow was followed by a rise in left atrial pressure and a fall in left ventricle work, due to a fall in both aortic pressure and cardiac output. The left ventricular function curves were lowered in proportion to the reduction of coronary flow. Further, a descending limb of the ventricular function curve appeared at filling pressures where previously no descending limb was present. It is important to note that with moderate restriction of coronary flow the impairment of the ventricular function curves was evident only at high filling pressures (See Ref. 2, Fig. 3). This is in agreement with the finding that, during a moderate coronary flow restriction, the coronary sinus oxygen saturation may not be reduced until high ventricular work levels are reached (Fig. 3).

The right ventricular function curve was lowered only when severe left ventricular failure and aortic hypotension were present. Constriction or occlusion of only the right coronary artery was done in two dogs with inconclusive results (2).

In two experiments the coronary sinus oxygen content was measured

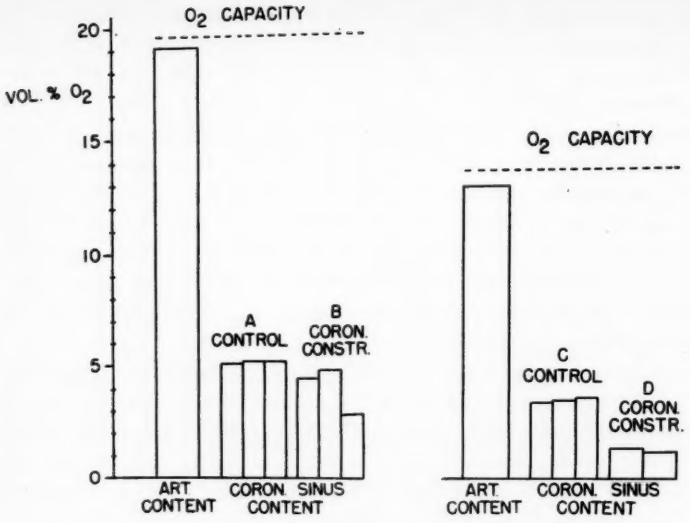

Figure 3. Exp. No. 116. Data from ref. 7, table I. Effect of moderate coronary artery constriction and/or lowered oxygen capacity of the blood, on the coronary sinus oxygen content. The coronary sinus samples in each set (A, B, C, D) were taken at various work levels (cf. Fig. 1). The coronary constriction applied was identical in B and D.—In A and C, without coronary constriction, the coronary sinus oxygen content was constant throughout the function curve (cf. Fig. 1), although in C it was lowered in proportion to the reduction of oxygen capacity. In B, with moderate coronary constriction, the coronary sinus oxygen saturation fell when a high work load was reached. In D, where both the anemia and the coronary constriction were applied, the coronary flow was markedly insufficient as demonstrated by the very low coronary sinus oxygen contents; a markedly lowered ventricular function curve resulted (ref. 7, fig. 5). See text.

during restriction of left coronary artery flow and was found to be lower than during the control condition (one of these experiments is reported in (7) and is illustrated in Figure 3). Thus, when coronary flow is restricted, the oxygen extraction from the coronary blood may be more complete.

During these experiments it was noted that, when the coronary flow tubing was acutely constricted, the coronary flow showed a temporary fall and then gradually increased to or towards its previous level, as long as the constriction was not made too severe. When the constriction was released, the coronary artery flow always maintained for some time a level higher than the control level.

Lowering of the Oxygen-Carrying Capacity of the Blood

When the hematocrit was lowered the coronary artery resistance decreased in rough proportion to the reduction of hematocrit. With marked hemodilution the coronary arteries seemed to be unable to dilate any further, as was evidenced by no further decrease of the coronary resistance even at high work levels. When the hematocrit was lowered beyond this limit, signs of impaired ventricular function appeared (7).

The coronary flow at various hematocrits and work loads seemed to adjust in such a way as to keep the coronary sinus saturation, and thus the partial pressure of oxygen, at a constant level (Fig. 3). When coronary restriction was superimposed, thereby restricting the compensatory increase of coronary flow during anemia, the oxygen extraction from the coronary blood was more complete and the coronary sinus oxygen saturation was markedly lower. This indicates a decrease in the partial oxygen pressure in the myocardium, and it is not surprising that myocardial failure and a descending limb occur (7). In Figure 3 the lowering of coronary sinus oxygen saturation indicates the degree to which the coronary flow fails to compensate for the lowered oxygen-carrying capacity of the blood.

Cardiovascular Effects of the Pericardium

Under normal circulatory conditions the pericardium does not exert any significant restraint on the diastolic expansion of the ventricles, i.e., moderate changes of the heart volume or fluid volume inside the pericardium do not significantly affect the intrapericardial pressure. With further distension of the pericardium a range is reached, however, where the diastolic expansion of the ventricles is restrained. The cardiovascular events during such conditions were studied (3, 4).

When pericardial tamponade was produced the intrapericardial pressure rose, along the increasingly steep pressure-volume curve of the pericardium. The atrial pressures increased but there was a fall in effective filling pressures (mean atrial minus end-diastolic pericardial pressure), and a fall of arterial pressures, cardiac output and ventricular stroke work. There was no evidence of inflow obstruction at the entrance of the veins into the pericardium. There was a close relationship betwen effective filling pressures and ventricular stroke work in the various degrees of tamponade. This is evidence that the

primary defect in tamponade is an interference with diastolic expansion of the ventricles (3). Similar changes were obtained during pericardial constriction (4).

In severe pericardial tamponade or constriction, the two atrial pressures are practically identical, even at high levels. The atrial pressures in this condition reflect the elevated intrapericardial pressure more than they reflect the effective filling pressures of the two ventricles.

In the presence of a normal or constricted pericardium the right ventricular function curve was lowered, when the left ventricle was stressed and caused to dilate. This suppression of the right ventricle function curve was totally or almost totally abolished when the pericardium was opened. Thus, if the left ventricle dilates to such an extent that the pericardium becomes stretched, the consequent increase in intrapericardial pressure will decrease the effective filling pressure and stroke work of the right ventricle. As a result of the suppressed right ventricular work, the pulmonary vascular pressures and blood volume are lower than they would be if the pericardium were absent (4).

In some experiments tricuspid or mitral regurgitation occurred at high degrees of filling without a pericardium, whereas in the same animal there was no regurgitation at similar or higher degrees of filling with a normal pericardium. The pericardium thus seems to prevent overdilatation of the atrio-ventricular ring and consequent valvular regurgitation. The role of this factor for the "descending limb" of the Starling curve has been discussed above and in (4).

Mechanism of Ventricular Output Balance

The normal circulation is a unique arrangement; two pumps are in series in a circuit, with no significant shunts between the two sides of the circuit (peripheral and pulmonary). The vessels connecting the two pumps can only to a certain extent accommodate shifts of blood volume from one part of the circuit to another. Therefore, the two ventricles have to maintain an average output balance, except during short transition periods. This balance has to be maintained also when the load on one or both ventricles is altered, or when the function of one or both ventricles is impaired.

During normal circulatory conditions the left atrial pressure is higher than the right. The experiments reported in (6) showed that the relationship between the ventricular filling pressures was altered when one ventricle was stressed or its function impaired; the filling pressure of the stressed or impaired ventricle was elevated in relation to that of the other ventricle. In the light of the demonstrated relationship between the filling pressure and the stroke work of each ventricle (1, 2, HENDERSON and PRINCE), it is likely that these alterations in filling pressure relationship serve to bring the ventricular outputs into balance. This may be the most important consequence of Starling's law.

In the presence of an inter-atrial septal defect the inter-atrial pressure gradient cannot be maintained at its normal level (DOW and MALONEY, 1951). Consequently, the mechanism described above, of maintaining ventricular output balance by means of filling pressure adjustments is abolished, and therefore the output of one ventricle is larger than that of the other (DOW and MALONEY, PEDERSON and WARBURG, 1952, HICKLER and GOODALE, 1954). This is further proof of the significance of the mechanism described above.

One clinical consideration may be mentioned. In conditions when the left ventricle is stressed or impaired, the left atrial pressure is elevated earlier and to a larger extent than the right atrial pressure (LEWIS *et al*, 1953, VARNAUSKAS, 1955). Right atrial pressure is thus a poor indicator of left ventricular function.

Cardiovascular Effects of Drugs

The described preparation offers several ways of assaying the cardiac and peripheral vascular effects of drugs (1, 5).

In response to a drug having a cardiac inotropic effect, the relation between atrial pressure and ventricular stroke work is altered. The comparison of ventricular function curves with and without the presence of a drug gives a quantitative measure of the drug's inotropic effect (1, 5). Changes in vascular tone can also be studied (5).

A quick assay and at least partial separation in time of the cardiac inotropic and the peripheral vascular effects of drugs can be accomplished with this preparation (5). When the left coronary artery is cannulated a delay is created between the peripheral vascular and the myocardial effects of a drug administered intravenously. Therefore,

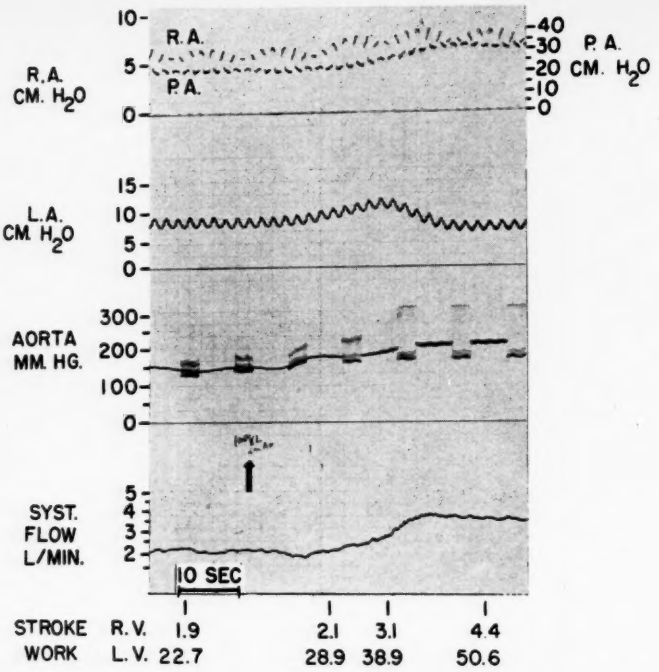

Figure 4: Exp. No. 164. Dog weight 23.6 kg. Heart weight 190 gm. Vagotomized. Pericardium intact. Demonstration of *peripheral vascular and cardiac inotropic effects of nor-epinephrine.* Tracing of pressures in right atrium (RA), pulmonary artery (PA), left atrium (LA) and aorta. Syst. flow = cardiac output minus coronary blood flow. The pressures are electrically integrated mean pressures; the aortic pressures are intermittently full and mean pressures. At the bottom are the calculated stroke work values of the right and left ventricles in grammeters. At the arrow synthetic norepinephrine (Levophed), 4.2 μ g./kg body weight, was given in the aortic tubing. Note the initial rise in aortic pressure and left atrial pressure with no significant change in cardiac output, (increased peripheral vascular resistance) and the following rise in cardiac output, further elevation of mean aortic pressure and larger aortic pulse pressure, with a fall in left atrial pressure (cardiac inotropic effect). See text.

the hemodynamic effects of the peripheral vascular action of the drug are evident well before the myocardial inotropic effect is added.

A somewhat similar time-dissociation method is possible even without cannulation of the coronary artery. Namely, if the drug is injected in the proximal part of the aorta instead of intravenously, it reaches the peripheral vascular bed before it reaches the coronary arteries;

the peripheral vascular effect of the drug will become evident before the cardiac inotropic effect. An example of this is shown in Figure 4. A similar type of "time-dissociation" with epinephrine was described by AHLQUIST (1954), who also compared the pressor effect of intravascular injections at various sites.

It is important to note that changes in peripheral vascular resistance and/or myocardial contractility always cause larger changes in left than in right atrial pressure. This emphasizes the desirability for measurement of left atrial pressure in studies of cardiovascular drugs.

For one of the "vasopressor" agents studied (Aramine) it was found that a relatively small dose improved myocardial contractility markedly and perhaps maximally, but had a relatively slight effect on peripheral vascular resistance; increase of the dose did not further improve myocardial contractility, but did increase peripheral vascular resistance and tone (5). Preliminary data in this laboratory indicate that this may also be the case with nor-epinephrine.

General Discussion

The knowledge of the relation between ventricular filling and ventricular work in the living animal, and of changes in this relationship during various circulatory conditions, provides a basis for a more complete understanding of the circulation and of muscular physiology in general (BLASIUS, 1872, FRANK 1895). Adjustments of muscular work by means of changes in fiber length may be of more functional importance in the heart muscle than in skeletal muscle. For in the heart muscle, all the fibers participate in every contraction, and the force of contraction cannot be altered by variation of the amount of contracting fibers (BOWDITCH, 1871). Further, the two ventricles have to maintain an average output balance, even when one ventricle is stressed or its function impaired; the response of each ventricle to variations in its filling pressure provides a simple servomechanism for this purpose.

Evaluation of "Starling's Law" in the Normal Circulation

The evaluation of "Starling's Law" in the normal or diseased man meets with several difficulties. Continuous measurements of cardiac output are still not possible in man. The measurement of the effective filling pressure of one or both ventricles is difficult. These difficulties could be avoided in the described preparation. Although the myocardium may not be in optimal condition, and the reactivity of the vasculature may be less than normal, the heart is certainly in a better state than in the classical heart-lung preparation. Limitations not withstanding, the preparation does allow more extensive studies on the behaviour of the heart during various conditions than is possible in man.

It has been stated that Starling's Law operates in the failing heart rather than in the normal (for references see 1). *The ventricular function curves obtained in the "normal" and the failing heart of our preparation indicate, however, that the Starling mechanism would operate in the normal heart more effectively than in the failing heart.*

A number of data give suggestive or firm support to the significance of the "Starling's Law" mechanism in the normal heart.

LAUSON, BLOOMFIELD and COURNAND (1946) studied the effect of respiration in patients without cardiovascular disease, measuring pressures in right auricle, right ventricle, central and antecubital veins, femoral artery, and the intrapleural space. During inspiration there was a rise in the "net filling pressure" of the right ventricle, and an increase in the net systolic pressure of the right ventricle, indicating an increase in right ventricle stroke volume during inspiration. Opposite changes took place during expiration. They concluded that the essential features of Starling's Law of the heart were operating under physiologic conditions. A similar relation between effective vena cava pressure and the measured right ventricle output during spontaneous respiration in dogs was demonstrated by BRECHER and HUBAY (1955).

On tilting of patients from recumbent to passive standing position, LAGERLÖF *et al* (1951) found a fall in both atrial pressures together with a simultaneous reduction of left and right ventricle stroke work. Measurements of intrapleural pressures were not done, but the diminished right atrial pressure amplitude during the heart cycle was taken as an indication that the net filling pressures were reduced. When the patients were tilted back to recumbent, the opposite changes were found.

The events during moderate exercise appear, on the surface, not in agreement with Starling's Law. Cardiac output, and to a lesser extent ventricular stroke work, may increase without elevations of atrial pressure (DEXTER *et al*, 1951) or heart size (LILJESTRAND, LYSHOLM and NYLIN, 1938). The Starling mechanism may well be masked by the increased heart rate, the systemic vasodilation (DEXTER *et al*) and hormonal factors (KAO and RAY, 1954). The ventricle probably shifts from one "Starling curve" to another, higher one.

The role of diastolic filling becomes evident in more severe exercise; this is regularly accompanied by increased heart size (LILJESTRAND *et al*). Data suggesting a relationship between central blood volume and stroke output during exercise were presented by ASMUSSEN and CHRISTENSEN (1939). Graded ergometer exercise was performed before and during experimentally produced pooling of blood in the legs; the latter condition was accompanied by a lower cardiac output and higher heart rate and A—V oxygen difference at identical levels of

oxygen consumption. This implies that the larger central blood volume makes possible a larger stroke volume and consequently a lower heart rate. Further, after heavy fluid loss, either by excessive perspiration (CHRISTENSEN, 1953) or after phlebotomy (BALKE *et al*, 1954), a standard heavy exercise is done with higher heart rate than in the control state.

The hemodynamic consequences of atrial septal defect (congenital or experimental) provide confirmation of Starling's Law (PEDERSON and WARBURG, 1952). The interatrial pressure gradient is partially or completely abolished (DOW and MALONEY, 1951); since the ventricular filling pressures cannot adjust as normally, the outputs of the two ventricles are not in balance (DOW and MALONEY, HICKLER and GOODALE, 1954, and others); instead, the output distribution now depends to a large extent on the relative resistances in the pulmonary and peripheral vascular beds. With closure of the defect, the outputs become balanced and a normal interatrial pressure gradient is established (HICKLER and GOODALE, 1954).

An interesting application of "Starling's Law" is provided by the data presented by RESTALL and SMIRK (1952). Normal or hypertensive subjects were given a fairly large dose of a ganglionic blocking agent; the arterial blood pressure could then be regulated at will by gradually submerging the subject in water. The authors suggest that the mechanism is increased ventricular filling by hydrostatic squeezing of the blood toward the heart. The same mechanism was suggested by TIGERSTEDT (1918) who also demonstrated that the blood pressure and cardiac output changed in the same direction. This principle has been applied to "controlled hypotension" in surgery (JAMES, COULTER and SAUNDERS, 1953).

Several investigators have failed to find a consistent correlation between right atrial pressure and cardiac output in man or dog. (For references, see 1.) This does not refute "Starling's Law" because right atrial pressure is not an indicator of left ventricular filling and function. It is of interest that HADDY *et al* (1949) found that the cardiac index in dogs showed a closer correlation with left atrial pressure than with right atrial pressure.

Heart Failure

It has been stated that heart failure may result simply from overdistending the ventricle, so that it reaches the "descending limb." The results obtained in this laboratory do not support such a concept. For the normal ventricular function curve did not show a descending limb, at least not in acute experiments, even when the filling pressures were brought to very high levels. Myocardial failure therefore must result from impairment of myocardial contractility; a lower ventricular function curve results, which in turn may show a descending limb. The high filling pressures occurring in failure are not the cause of but the direct or indirect result of the circulatory failure.

It is important to note that the impairment of myocardial function, if only moderate, may not be evident from examination of only the lower part of the ventricular function curve (2). A clinical counterpart is that patients with moderate heart failure may not have symptoms or exhibit abnormal circulatory data, unless performing moderate or severe exercise.

It was possible to produce unilateral ventricular failure in the dog (2, 7). That this occurs also in man has been amply demonstrated (LEWIS *et al*, 1953, VARNAUSKAS, 1955). This emphasizes the need for measurements of left atrial or pulmonary capillary venous pressures at rest and during exercise.

When one ventricle becomes acutely stressed, the shifts of blood volume and consequent changes in the relation between the two atrial pressures usually serve to decrease the stroke work of the unstrained ventricle and either increase or leave unchanged the stroke work of the strained ventricle; this will bring the outputs back into balance. If, however, the strained ventricle is diseased to such an extent that it already is operating on a marked "descending limb," this "balancing mechanism" may not be able to readjust the two outputs to equal levels, and circulatory collapse may result.

Effect of Drugs

The data presented in (5) suggest that the beneficial effect of vasopressor drugs in cardiogenic shock is due mainly to the positive cardiac inotropic action. It has been stated that an "ideal" vasopressor drug should have only a peripheral vascular effect. The author be-

lieves, however, that if a patient is in cardiogenic shock, and in danger of pulmonary edema, an agent which solely causes peripheral vasoconstriction would raise the left atrial pressure still further and precipitate pulmonary edema (SARNOFF and BERGLUND, 1952).

The amount of coronary blood flow is altered after the administration of a large variety of drugs. These changes in coronary blood flow may, however, be due to the concomitant changes in ventricular work and oxygen consumption rather than to primary and direct effects on the coronary vasculature (5, 7, and FOLKOW, FROST and UVNÄS, 1949). The term "coronary vasodilator" has probably been attached to many drugs, without sufficient evidence of their direct coronary vasodilator action.

There are different opinions as to the mechanism of the positive inotropic effect of drugs, e.g., adrenaline. The increased work at a given or lower filling pressure could be due to increased diastolic fiber length at that filling pressure, and/or increased force of contraction at a given fiber length. That the latter of these two mechanisms exists and probably dominates, is indicated by the following findings. 1) The length-tension relationship and the "viscosity" of a heart-muscle strip at rest are unchanged, while the contractile force is increased by adrenaline (LUNDIN). 2) Preliminary experiments in this laboratory indicate that Aramine, a drug with structure and action similar to nor-adrenaline (5), increases ventricular stroke work, even when the diastolic volume is markedly restricted by means of severe pericardial constriction. 3) By means of a strain-gauge arch sutured directly to the ventricular wall, the "heart force" of a segment of heart muscle with relatively fixed fiber length can be recorded; nor-epinephrine and several other "pressor amines" produce increased "heart force" (COTTEN, 1953). 4) The heart size usually decreases after the administration of a drug with positive inotropic effect.

"Starling's Law" as an Integrating Mechanism in the Regulation of Cardiac Output

The present investigation has demonstrated that there is always a relation between ventricular filling pressure and ventricular work, and this relation can be described as the "ventricular function curve." The shape and height of this can be altered by many factors, such as restriction of coronary blood flow and various hormones or drugs.

There is therefore no "absolute" ventricular function curve, but rather a "family" of curves. The frequent demonstration of changes in ventricular work or output due to factors other than diastolic fiber length (HAMILTON, 1953, KAO and RAY, 1954, SJÖSTRAND, 1953, and others) does therefore not disprove "Starling's Law;" it means that the ventricle has shifted from one curve to another. The concept of a family of curves may add to the understanding of, and to a more quantitative estimation of, these changes.

Neither the normal nor the failing heart depends only on variations of fiber length or any other single factor for the regulation of cardiac output. The relationship between diastolic fiber length and ventricular stroke work, in addition to furnishing a mechanism for regulation of cardiac output, provides a simple servo-mechanism for maintaining ventricular output balance.

Summary

During the nineteenth century it was demonstrated that in skeletal muscle there is a relation between resting fiber length and tension, and the force of the contraction. Studies on isolated heart muscle strips, on isolated perfused hearts from poikilothermic or mammalian animals, and on mammalian heart-lung preparations have demonstrated the existence of the same relationship in heart muscle. This relationship is generally known as Starling's law of the heart. The classically conceived Starling curve shows increased ventricular work with increased ventricular diastolic volume; beyond a certain volume, there is, however, a marked decrease in work (the descending limb). The validity and significance of this relationship in the living animal and man has been a matter of debate.

Present Investigation

In the anesthetized open- or closed-chest dog there was consistently found a relationship between the filling pressure and mechanical stroke work of each ventricle. This relationship is described as the ventricular function curve. The height and shape of the ventricular function curve is altered by various factors, i.e., there is a "family" of curves for any given ventricle.

The "normal" ventricular function curve shows a steep rise, i.e., small increases of ventricular filling pressure elevate the ventricular stroke work markedly. At higher levels the curve may flatten off (slight or no change in work with large increments in filling pressure); even at high atrial pressures the normal curve did not show a descending limb.

Restricted oxygen transport to the heart by coronary constriction or severe anemia resulted in lower function curves (impaired function) of one or both ventricles. These impaired function curves sometimes had significant descending limbs.

The response of the coronary vasculature to lowered oxygen content of the arterial blood is vasodilation. The increased coronary flow is

the quantitatively most important compensatory mechanism for decreased oxygen-carrying capacity of the blood; increased oxygen extraction becomes an important factor when the increase of coronary blood flow is inadequate.

The pericardium normally does not restrain the diastolic filling of the ventricles. It restrains diastolic filling if it is stretched by intrapericardial fluid or by a distended ventricle, or if it is constricted.

The relation between left and right ventricular filling pressures is altered when one ventricle is stressed or its function impaired. This change in filling pressure relationship serves to maintain an average balance of left and right ventricle output.

The effect of cardiovascular drugs can be studied, in this preparation, both as regards their cardiac and their peripheral vascular effects. The cardiac effect can be quantitatively measured by means of the ventricular function curve.

The existence and role of the relationship between diastolic fiber length and ventricular work in man during normal and abnormal conditions is discussed. It is believed that this relationship is one of several mechanisms available for regulation of cardiac output, and that it provides a simple servo-mechanism for maintaining ventricular output balance.

References

Numbers 1—9: See page 3—4.

AHLQUIST, R. P.: Adrenergic Drugs. In V. A. DRILL: Pharmacology in Medicine. New York. McGraw-Hill, 1954.

ASMUSSEN, E. and E. H. CHRISTENSEN. Skandinav. Arch. f. Physiol. 1939: *82*, 185.

BALKE, B., G. P. GRILLO, E. B. KONECCI and U. C. LUFT. J. Appl. Physiol. 1954: *7*, 231.

BLASIUS, W. Verhandl. d. phys.-med. Gesellsch. Würzburg. 1872: *2*, 49.

BOWDITCH, H. P. Leipzig. Arbeit Physiol. Anst. 1871: 652.

BRECHER, G. A. and C. A. HUBAY. Circulation Research 1955: *3*, 210.

COTTEN, M. DE V. Am. J. Physiol. 1953: *174*, 365.

CHRISTENSEN, E. H. Personal Communication 1953.

DEXTER, L., J. L. WHITTENBERGER, F. W. HAYNES, W. T. GOODALE, R. GORLIN and C. G. SAWYER. J. Appl. Physiol. 1951: *3*, 439.

DOW, J. W. and J. V. MALONEY. Am. J. Med. 1951: *10*, 235.

DRESER, H. Arch. exper. Path. u. Pharmakol. 1887: *24*, 221.

EVANS, C. L. and Y. MATSUOKA. J. Physiol. 1915: *49*, 378.

FICK, A. Untersuchungen über Muskel-arbeit, Basel, Georg, 1867.

FRANK, O. Ztschr. f. Biol. 1895: *32*, 370.

FOLKOW, B., J. FROST and B. UVNÄS. Acta physiol. Scandinav. 1949: *17*, 201.

HADDY, F. J., G. S. CAMPBELL, W. L. ADAMS and M. B. VISSCHER. Am. J. Physiol. 1949: *158*, 89.

HALES, STEPHAN. Statical Essays. II. Containing Haemastatics; or An Account of some Hydraulick and Hydrostatical Experiments Made on the Blood and Blood-Vessels of Animals, London, Innys and Manby, 1733.

HAMILTON, W. F. Circulation 1953: *8*, 527.

HARVEY, W. Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus, 1628. Springfield, Ill. Charles C. Thomas, 1949.

HEIDENHAIN, R. Mechanische Leistung, Wärmeentwicklung und Stoffumsatz bei der Muskelthätigkeit. Ein Beitrag zur Theorie der Muskelkräfte, Leipzig Breitkopf und Härtel, 1864.

HENDERSON, Y. Am. J. Physiol. 1906: *16*, 325.

HENDERSON, Y. and A. L. PRINCE. Heart 1914: *5*, 217.

HICKLER, R. B. and W. T. GOODALE. Fed. Proc. 1954: *13*, 70.

HOWELL, W. H. and F. DONALDSON. Philos. Trans., London 1884: *175*, 139.

JAMES, A., R. L. COULTER and J. W. SAUNDERS. Lancet 1953: *1*, 412.

JERUSALEM, E. and E. H. STARLING. J. Physiol. 1910: *40*, 279.

JOHANSSON, J. E. and R. TIGERSTEDT. Skandinav. Arch. f. Physiol. 1889: *1*, 331.

KAO, F. F. and L. H. RAY. Am. J. Physiol. 1954: *179*, 255.

KATZ, L. N. Am. J. Physiol. 1928: *87*, 348.

KNOWLTON, F. P. and E. H. STARLING. J. Physiol. 1912: *44*, 206.
KROGH, A. Scandinav. Arch. f. Physiol. 1912: *27*, 126.
KROGH, A. and J. LINDHARD. Ibid. 1912: *27*, 100.
KUNO, Y. J. Physiol. 1915: *50*, 1.
LAGERLÖF, H., H. ELIASCH, L. WERKÖ and E. BERGLUND. Scand. J. Clin. & Lab. Invest. 1951: *3*, 85.
LAUSON, H. D., R. A. BLOOMFIELD and A. COURNAND. Am. J. Med. 1946: *1*, 315.
LEWIS, B. M., H. E. J. HOUSSAY, F. W. HAYNES and L. DEXTER. Circulation Research 1953: *1*, 312.
LILJESTRAND, G., E. LYSHOLM and G. NYLIN. Skandinav. Arch. f. Physiol. 1938: *80*, 265.
LUNDIN, G. Acta physiol. scandinav. 1944: *7*, Suppl. 20.
MARTIN, H. N. John Hopkins Biol. Lab. Studies. 1883: *2*, 119.
DI PALMA, J. R. and A. R. REISS. Am. J. Physiol. 1948: *155*, 327.
PATTERSON, S. W., H. PIPER and E. H. STARLING. J. Physiol. 1914: *48*, 465.
PATTERSON, S. W. and E. H. STARLING. J. Physiol. 1914: *48*, 357.
PEDERSEN, A. and E. WARBURG. Cardiologia 1952: *21*, 517.
RESTALL, P. A. and F. H. SMIRK. Brit. Heart J. 1952: *14*, 1.
ROHDE, E. Arch. exper. Path. u. Pharmakol. 1912: *68*, 401.
ROY, C. S. J. Physiol. 1879: *1*, 452.
ROY, C. S. and J. G. ADAMI. Brit. M. J. 1888: *2*, 1321.
SARNOFF, S. J. and E. BERGLUND. Am. J. Physiol. 1952: *170*, 588.
SJÖSTRAND, T. Physiological Reviews 1953: *33*, 202.
STARLING, E. H. The Linacre Lecture on the Law of the Heart. Given at Cambridge, 1915. London, Longmans, Green & Co., 1918.
STARLING, E. H. and M. B. VISSCHER. J. Physiol. 1927: *62*, 243.
STRAUB, H. Deutsche Archiv. f. Klin. Medizin, 1914: *115*, 531.
STRAUB, H. Ibid. 1914: *116*, 409.
TIGERSTEDT, C. Skandinav. Arch. f. Physiol. 1918: *36*, 322.
VARNAUSKAS, E. Scandinav. J. Clin. & Lab. Invest. 1955: *7*, Suppl.
WALLER, A. D. Arch. Anat. Physiol. 1878: 525.
WEBER, Eduard. In Rudolph Wagner — Handwörtenbuch der Physiologie mit Rücksicht auf physiologische Pathologie. 1846: *3*, part 2. Braunschweig: Vieweg und Sohn.
WIGGERS, C. J. Am. J. Physiol. 1914: *33*, 382.